At the outset, it is noted that the Examiner made the first Action in this application final, notwithstanding the fact that Applicants had submitted a §132 Declaration not previously considered in the parent application. It would seem, since new evidence was of record which was not submitted during prosecution of the parent application, that the first Office Action properly should have been a non-final Office Action. Accordingly, if the Examiner elects not to allow this application, at the least, she is respectfully requested to vacate the finality of the previous Office Action as it was clearly improper.

Turning now to the outstanding rejections, Claims 1-3 stand rejected under 35 U.S.C. §102(b) as assertedly being anticipated by Ferreira et al or Oluyomi et al. This rejection is respectfully traversed.

First, turning to Ferreira et al, this reference essentially relates to the use of various peptides and pharmaceutical compositions containing for the treatment of pain. However, contrary to the Office Action, the reference does not teach or suggest the use of such peptides for inhibiting inflammation. It would appear, based on the Office Action, that the Examiner's reasoning is that the rejection is proper since the reference is dealing with inflammatory related pain. However, the conclusion of the Examiner is respectfully traversed.

While the Examiner is correct that inflammation can be associated with pain, it is unreasonable to conclude that a compound which inhibits pain, even if it is associated

with inflammation, would inhibit inflammation. In other words, the fact that a compound inhibits pain does not reasonably suggest that this compound would elicit an anti-inflammatory response as required by the claimed methods of therapy. Rather, the reference merely reports a family of peptides which purportedly effectively can antagonize hyperalgesia induced by inflammatory agents. However, the reference does not indicate that such peptides function as anti-inflammatory agents. Thus, Applicants respectfully submit that the anticipatory rejection based on this reference is improper since it fails to teach or suggest the anti-inflammatory activity of Lys-Pro-Val. Rather, the reference merely suggests the analgesic, i.e., anti-pain, effects of such peptides, e.g., in response to injected inflammatory agents.

Turning now to Oluyomi et al, this reference also fails to anticipate or render obvious the subject invention. As previously argued and as acknowledged by the Examiner at page 3 of the Office Action, the Oluyomi et al reference properly should be read together with Hiltz et al since the authors refer substantially to the results of this earlier (1991) reference. With respect to such conclusion, the Examiner further states in the Office Action that Hiltz et al is a 1991 reference, whereas Oluyomi et al is a 1994 reference. It is unclear why the Examiner is referring to the publication dates since she has acknowledged that both references should be read together. Moreover, it is quite clear that Oluyomi et al in their 1994 publication gave considerable weight to Hiltz et al

since they base many of their conclusions on this reference. Therefore, even in 1994, i.e., three years later, these results were still regarded to be significant.

For the reasons previously argued, Hiltz et al clearly teaches against the subject invention since it is explicit that the levorotatory form of proline in the Lys-Pro-Val sequence is significant to an anti-inflammatory activity. For example, in the results section at page 769, Hiltz et al indicates that a peptide comprising the dextrarotatory form of proline "had no significant effect on inflammation". Moreover, in the discussion section of the reference, when they summarize their conclusions, they state the following: "This finding underlines again the importance of L-Pro to the anti-inflammatory responses." Moreover, at page 770, right-hand column, the authors further note that loss of activity (anti-inflammatory activity) with D-Pro^{12} substitution has been described previously. Therefore, it is quite clear, as explained in the previously submitted §132 Declaration, that Hiltz et al are not ambiguous in their conclusions as to the lack of anti-inflammatory activity of the subject peptides. To the contrary, they expressly note that L-Pro is significant to the anti-inflammatory activity of the studied peptides.

With respect thereto, the Examiner states in the Office Action that it is not clear which phase of inflammation Hiltz et al is referring to when they say it is inactive. However, the asserted lack of ambiguity is irrelevant based on the reference. Indeed, based on the express statements excerpted above, the authors are unambiguous in their

conclusions, i.e., the fact that L-Pro is significant for anti-inflammatory activity. They do not equivocate their conclusions and do not suggest that their results are dependent upon the particular phase of inflammation.

Turning now to the Oluyomi et al reference cited in the anticipatory rejection, Applicants respectfully submit that a clear and careful review of the reference further indicates that Oluyomi et al also fails to anticipate or render obvious the claimed therapeutic methods. In particular, the reference would not fairly suggest the anti-inflammatory activity of the Lys-D-Pro-Val tripeptide sequence.

Again, Applicants respectfully submit that this reference is primarily directed to evaluation of the anti-nociceptive activity of peptides related to interleukin-1β, i.e., the anti-pain or anti-analgesic activity of such peptides. This activity is evaluated in tests conventionally used to elicit pain as described at page 132 of the reference. These tests include, in particular, the rat paw test. Based on the results, the authors note that the disclosed peptides, which include Lys-D-Pro-Val NH_2 may represent peripherally acting analgesic compounds. They further note that such peptide is only active in the late phase of formalin-induced nociceptive response and that such peptide is relatively less potent in comparison to peptides in a first group (see page 137, right-hand column of the reference). Therefore, based on their conclusions, they suggest that the peptides studied

in the reference may be useful for inhibition of pain. However, they do not suggest the anti-inflammatory activity of such peptides.

It would appear that the Examiner has come to this conclusion based on the statement at page 137, left-hand column, lines 1-6, wherein the authors state "the peripheral anti-inflammatory activity of this peptide as reported by Hiltz and Lipton (1989) and its analogs (Hiltz et al, 1991)." However, as stated in the §132 Declaration of record, Hiltz et al does not teach or suggest the anti-inflammatory activity of the subject peptide. Indeed, the reference teaches exactly the reverse. Therefore, one of ordinary skill, reading this reference together with the references from which they base their conclusions, would be of the opinion that such peptide would not elicit significant anti-inflammatory activity. Moreover, one of ordinary skill, reading the reference, would be expected to read the reference in its entirety. For example, the very next paragraph refers to the same 1991 Hiltz et al reference and they state as follows: "L-Pro^{12} of α-MSH is though to be important in the anti-inflammatory response." Also, the authors further go on to state that alteration of the disclosed tripeptides via D-substitution while increasing stability and potency and duration of action (anti-nociceptive activity) results in loss of anti-inflammatory activity. Therefore, Applicants respectfully submit that the reference does not reasonably suggest the subject invention. To the contrary, the reference is directed to the study of various peptides, includes Lys-Pro-Val, for inhibition

of pain. However, the reference does not fairly suggest the use of such peptide for inhibiting inflammation as claimed in the present invention.

It would again appear, based on the statement at page 4 of the Office Action, that the Examiner has improperly equated anti-inflammatory activity to an analgesic. Specifically, the Examiner quote the following statement from Oluyomi et al: "We conclude that useful analgesics may be developed from peptides containing the sequence Lys-D-Pro-X." Thus, the 1994 reference does show and believe that peptides containing D-pro are anti-inflammatory. However, the Examiner's conclusion is improper. Contrary to such assertion, an analgesic cannot be equated to an anti-inflammatory agent. For the convenience of the Examiner, a definition of analgesic from Dorlands Illustrated Medical Dictionary is attached to this Reply. As previously argued, "analgesic" means relieving pain. It does not equate to anti-inflammatory action, notwithstanding the Examiner's seeming conclusion to the contrary. Also, while the Examiner is correct that inflammation can be associated with pain, this again does not mean that a compound which inhibits pain would necessarily have any significant effect on inflammation.

Also, it is noted that the Examiner has failed to consider various references cited in the Declaration since they apparently were not readily available for review. For the convenience of the Examiner, Applicants will later provide copies of these references. However, these references were sufficiently described in the Declaration and substantiate

Applicants' arguments, namely the reasonable expectation that the L-Pro amino acid had been thought to be required for anti-inflammatory activity of the peptides disclosed in Hiltz et al.

Further, Claims 4, 7-10 and 18 stand rejected under 35 U.S.C. §103 as being obvious over Ferreira et al. This reference has been discussed above. For the reasons set forth therein, the reference merely relates to the analgesic activity of various peptides. However, it does not teach or suggest the use of such peptides for inhibiting inflammation as claimed herein. Withdrawal of this rejection is therefore respectfully requested.

Claims 5, 6 and 19 stand rejected under 35 U.S.C. §103 as assertedly being unpatentable over the combination of Ferreira et al in view of Lipton and Oluyomi et al. Ferreira et al has been discussed above, as has Oluyomi et al. For the reasons set forth therein, these references, separately and in combination, fail to teach or suggest the invention. To the contrary, they merely relate to the use of various peptides for inhibition of pain. However, they do not teach or suggest the activity of the subject tripeptide as an anti-inflammatory agent. Moreover, such activity is particularly surprising based on references discussed in the Oluyomi et al reference, which would have reasonably suggested the contrary.

The deficiencies of Ferreira and Oluyomi et al are not cured by Lipton. This reference does not teach or suggest the anti-inflammatory activity of the subject

tripeptide, i.e., Lys-Pro-Val, wherein proline is in its dextrarotatory form. Rather, the reference substantially relates to peptides in their conventional L-form and protected versions of such peptides for reducing fever and inflammation. Therefore, based on the foregoing, withdrawal of the §103 rejection of Claims 5, 6 and 19 based on Ferreira et al in view of Lipton and Oluyomi et al is respectfully requested.

Claims 1-11 and 16-19 stand rejected under 35 U.S.C. §103 as being unpatentable over Ferreira et al, in view of Norlund et al, Lipton and Remington's Pharmaceutical Sciences, and Oluyomi et al. The Ferreira et al, Lipton, and Oluyomi et al references have been discussed above. For the reasons set forth therein, these references fail to teach or suggest the anti-inflammatory activity of the specific tripeptide sequence which contains proline in its dextro rotatory form. The deficiencies of the rejection are further not cured by Remington's Pharmaceutical Sciences and Norlund et al.

Norlund et al relates to the treatment of dermatitis by topical application of a composition including a melanocyte-stimulating hormone. However, the reference fails to teach or suggest the anti-inflammatory activity of the specific tripeptide, i.e., Lys-Pro-Val, wherein Pro is in its dextrarotatory form. Similarly, Remington's Pharmaceutical Sciences fails to teach or suggest the anti-inflammatory activity of the subject peptide. Rather, this is a general textbook relating to various pharmaceutical compositions and modes of administration. Therefore, the cited combination of references also fails to

teach or suggest the invention since there is nothing which would allow one to reasonably infer the anti-inflammatory activity of the subject tripeptide. Withdrawal of the §103 rejection of Claims 1-11 and 16-19 based on Ferreira et al, in view of Norlund et al, Lipton, Remington's Pharmaceutical Sciences, and Oluyomi et al is therefore respectfully requested.

Finally, Claims 1-3, 5-11 and 16-19 are rejected under 35 U.S.C. §103 as assertedly being unpatentable over Oluyomi et al (1994) in view of Norlund et al, Lipton and Remington's Pharmaceutical Sciences. All of these references have been discussed above. Essentially, the references, separately and in combination, fail to teach or suggest the anti-inflammatory activity of the subject peptide. Rather, the references merely suggest the anti-nociceptive, i.e., analgesic, activity of the subject tripeptide. The only references which relate to anti-inflammatories do not teach or suggest the anti-inflammatory activity of the specific tripeptide of the invention. Moreover, for the reasons set forth above, this is an unexpected discovery based on the fact that the prior art would have reasonably suggested that the levorotatory form of proline was significant to the anti-inflammatory activity of MSH-related peptides.

Therefore, based on the foregoing, withdrawal of the §103 rejection of Claims 1-3, 5-11 and 16-19 based on Oluyomi et al in view of Norlund et al, Lipton and Remington's Pharmaceutical Sciences is respectfully believed to be in order.

Based on the foregoing, this application should be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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